

**REMARKS**

Claims 1-17 were pending in the instant application. This Amendment follows a personal interview held January 19, 2005 between Applicants' undersigned attorney, Patrick T. Skacel, and Examiner Cook. The courtesies extended Applicants' attorney during the Examiner interview are sincerely appreciated. The remarks presented in this Amendment make of record and further address the issues discussed during the interview. By this Amendment, Applicants have amended claims 1, 7, 8, and 11 as discussed during the interview. Support for the claim amendments can be found in the specification and claims as originally filed. Applicants assert that the present Amendment does not introduce any new matter, and thus, its entry is requested. Upon entry of the present Amendment, therefore, claims 1-17 will remain pending and under examination.

**The November 30, 2004 Final Office Action**

**Withdrawal of previous amendments**

The Examiner withdrew the previous enablement and indefiniteness rejections in view of Applicants' reply filed June 15, 2004. Applicants acknowledge and appreciate the withdrawal of these rejections.

**Examiner's rejection under 35 U.S.C. §112, first paragraph**

The Examiner rejected claims 1-8 and 11-17 under 35 U.S.C. §112, first paragraph as allegedly lacking adequate written description. Specifically, the Examiner stated that although there is support for the word "inhibition" in the specification (e.g. at page 3, line 5), the Examiner sees no support for the word "reducing."

Appl. No. 09/926,286  
Amdt. Dated January 31, 2005  
Reply to Final Office Action of August 31, 2004

In response, Applicants point out that the specification does in fact refer to a “reduction of invasion” (page 5, lines 12-13) and “a reduction in cell migration” (page 12, lines 24-25). Nevertheless, without conceding the correctness of the Examiner’s position, but to expedite allowance of the subject application, Applicants have amended claim 1 to refer to “inhibiting” invasiveness and/or migration, rather than “reducing,” making the language consistent with that for which the Examiner has acknowledged adequate support in the specification. Corresponding amendments to claims 7, 8, and 11 also have been made. Applicants note that these claim amendments were presented to the Examiner and discussed during the Examiner interview. Applicants believe that the amendments fully overcome the Examiner’s concerns with respect to written description, and thus respectfully request that the rejection under 35 U.S.C. §112, first paragraph be withdrawn.

Examiner’s rejection under 35 U.S.C. §103

The Examiner maintained the previously set forth rejection of claims 1-17 under 35 U.S.C. §103 as being obvious over the Berry, et al. reference (WO 99/06040) alone, for the reasons set forth in previous Actions.

In response, Applicants respectfully traverse the rejection. Applicants believe that the Examiner’s application of the Berry reference to the present claims continues simply to be incorrect. Berry, et al. on its own, which refers to a synergistic combination of a tocotrienol and ALA (or its derivatives), does not provide any motivation to use ALA alone for inhibiting or reducing invasiveness and/or migration of malignant cells. In that regard, the portions of the reference to which the Examiner has pointed do not in fact support the position the Examiner has

taken. For example, the Examiner has asserted that Berry's teaching of a synergistic effect of the combination of a tocotrienol and ALA (at page 13, lines 12-16) provides ample motivation to use ALA alone. In Applicants' view, however, a fair reading of this passage instead leads one to conclude that it would not be beneficial to even try ALA outside of the recited combination in any effort to achieve beneficial results. This paragraph, among others, clearly states the advantage of using a combination of ingredients, as opposed to using either ingredient on its own. In at least this instance, therefore, the Berry reference actually teaches away from the claimed invention. Moreover, there is nothing in any other part of the reference to suggest effectiveness of ALA alone. It appears clear that the Berry reference, considered in its entirety, simply does not provide either the motivation or desirability to practice the claimed invention.

Furthermore, Applicants point out the following with respect to the Berry reference. The synergistic effect of tocotrienols and alpha lipoic acid is explained on page 16, line 16 to page 17, 1<sup>st</sup> paragraph. There is affirmed that lipoic acid induces a rapid reduction of oxidized tocotrienol thereby increasing its anti-oxidative capability. In addition, the reference teaches that lipoic acid may restore intracellular glutathione levels, thus "boosting glutathione-related detoxification mechanisms thereby postponing or preventing the incidence of squamous carcinomas" (page 18, lines 13-23).

In both cases, lipoic acid behaves as expected in view of its well known anti-oxidant properties (lipoic acid is also known to maintain vitamin E in a reduced state - see for example Packer *et al.*, Free Radical Biology and Medicine, 19, 2: 227-250). A fair reading of Berry would bring a person skilled in the art to conclude that lipoic acid synergizes with tocotrienol by making the latter readily available to scavenge free radicals (*"tocotrienols are more readily available to*

Appl. No. 09/926,286  
Amdt. Dated January 31, 2005  
Reply to Final Office Action of August 31, 2004

*more cellular compartments to interact with free radicals in those compartments"*, page 16 - lines 21-22). Therefore, tocotrienol is the active substance primarily contributing to the beneficial effects observed with the Berry composition, while lipoic acid supports or strengthens tocotrienol radical scavenging activity (*"It is believed that the synergistic effect of tocotrienols and alpha lipoic acid is the result of the phytol side chain of tocotrienols which provides enhanced lipophilic mobility and intermembrane transferability to the tocotrienols"* - page 16 , lines 16-19). The experimental evidence provided by Berry *et al.* confirm this conclusion. Significantly, tocotrienols are tested alone (see Tables 1 and 2, page 23), in contrast to lipoic acid, which is always used in combination. Furthermore, the assays described in the Berry reference are in no way predictive of an antitumor activity.

Consequently, a skilled person would not seriously contemplate using lipoic acid alone to treat malignancies, even less to treat metastases. Accordingly, the Berry reference alone does not render obvious any of the claims of the present application. Thus, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1-17 under 35 U.S.C. §103.

#### **The January 19, 2005 Interview**

Agreement was not reached on allowance during the interview held on January 19, 2005, as reflected in the Interview Summary prepared by Examiner Cook. At the interview, Applicants' undersigned attorney and Examiner Cook discussed the above-noted written description requirement, the claims now presented herein to overcome the rejection, and the position of the Applicant that the claims are not rendered obvious by the Berry reference. Applicants' undersigned attorney agreed to consider filing the RCE that now accompanies this

Appl. No. 09/926,286  
Amdt. Dated January 31, 2005  
Reply to Final Office Action of August 31, 2004

Amendment, to make the present claim amendments to overcome the written description rejection and to further argue in traverse of the obviousness rejection based on the Berry reference of record.

In light of the above remarks and claim amendments, Applicants believe that the Examiner's rejections set forth in the August 31, 2004 Final Office Action have been fully overcome and that the present claims fully satisfy the patent statutes. Applicants therefore believe that the application is now in condition for allowance. The Examiner is invited to telephone the undersigned if it is deemed to expedite allowance of the application.

Respectfully submitted,



Date: January 31, 2005

Patrick T. Skacel  
Registration No. 47,948  
Attorney for Applicants  
Rothwell, Figg, Ernst & Manbeck, P.C.  
1425 K Street, N.W., Suite 800  
Washington, DC 20005  
Telephone: (202) 783-6040  
Fax: (202) 783-6031

2965-159.amd02..wpd